IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/665,552	Confirmation No.	: 6176
First Named Inventor	: Johannes BARTHOLOMAEUS		
Filed	: September 22, 2003		
TC/A.U.	: 1615		
Examiner	: Susan T. Tran		
Docket No.	: 029310.50777CP		
Title	: Oral Administration Form for Administering a Fixed Tramadol and Diclofenac Combination		

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the Office Action mailed October 29, 2010, rejecting claims 1-4, 6, 7, 9-26 and 29, which are reproduced in the Claims Appendix of this brief.

A four-month extension of the deadline for filing the Appeal Brief is respectfully requested pursuant to 37 C.F.R. § 1.136(a) and the appropriate extension of time fee is submitted herewith.

I. REAL PARTY IN INTEREST

Grünenthal GmbH is the real party in interest of the present application.

II. RELATED APPEALS AND INTERFERENCES

Neither the Appellants' legal representative nor Grünenthal GmbH know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-4, 6, 7, 9-26 and 29 are under final rejection. Claims 5, 8, 27, and 28 have been canceled.

IV. STATUS OF AMENDMENTS

No claim amendments were filed subsequent to the final rejection of claims 1-4, 6, 7, 9-26 and 29 in the Office Action mailed October 29, 2010.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to an oral administration unit comprising a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second active substance diclofenac or a pharmaceutically acceptable salt thereof.[1] In the oral administration unit, the two active substances are present in separate subunits so as to not impair the release profiles of the two active substances.[2] The separate subunits are present in multiparticulate form.[3] In the oral administration unit, the active substances tramadol and diclofenac are also contained in a quantitative ratio of 1:4 to 4:1.[4] The tramadol and the

[1] See, for example, specification, page 2, lines 27-29.
[2] See, for example, specification, page 2, lines 19-26 and 29-31.
[3] See, for example, specification, page 3, lines 23-24.
[4] See, for example, specification, page 3, lines 12-14.

diclofenac are released in amounts of more than 70% and more than 60% by weight, respectively, within 8 hours.[5]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-4, 6, 7, 9-26 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4,690,927 ("Voss et al.") in view of Mok et al., "Analgesic Effect of Tramadal and Diclofenac in Combined Use," *American Society for Clinical Pharmacology and Therapeutics*, 1996, p. 132 ("Mok et al.") and U.S. Patent No. 5,041,430 ("Addicks et al."), and U.S. Patent No. 5,597,560 ("Bergamini et al.") or U.S. Patent No. 5,679,660 ("Bodley et al.").

Claims 1-4, 6, 7, 9-26 and 29 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,516,803 ("Raffa") in view of Mok et al. and Addicks et al., and Bergamini et al. or Bodley et al.

VII. ARGUMENT

Rejection under 35 U.S.C. § 103(a) over Voss et al. in view of Mok et al. and Addicks et al., and Bergamini et al. or Bodley et al.

Claims 1-4, 6, 7, 9-26 and 29

Appellants surprisingly observed that tramadol-HCl and diclofenac-Na form a sparingly soluble compound, which reduces the bioavailability of both tramadol and diclofenac and necessitates the use of higher dosages to compensate for the reduced solubility/bioavailability. See specification at paragraph [0006]. Accordingly, Appellants sought an appropriate formulation to overcome the problem of reduced solubility of the combination of tramadol and diclofenac. The presently claimed oral administration unit solves this problem of reduced solubility.

The presently claimed oral administration unit comprises a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second

[5] See, for example, specification, page 4, lines 16-20 and Fig. 1.

active substance diclofenac or a pharmaceutically acceptable salt thereof. The two active substances are present in separate subunits so as to not impair the release profiles of the two active substances. The separate subunits are present in multiparticulate form. The active substances tramadol and diclofenac are contained in a quantitative ratio of 1:4 to 4:1. The tramadol and the diclofenac are released in amounts of more than 70% and more than 60% by weight, respectively, within 8 hours.

Appellants have unexpectedly discovered that the presently claimed oral administration unit including separate subunits containing tramadol or a pharmaceutically acceptable salt thereof, and diclofenac or a pharmaceutically acceptable salt thereof, respectively, does not impair the release profiles or reduce the bioavailabilities of the tramadol and diclofenac, respectively. The released amounts and the release profiles of tramadol and diclofenac from the presently claimed oral administration unit correspond to the released amounts and release profiles of an administration unit containing tramadol only and an administration unit containing diclofenac only.

Voss et al. discloses a pharmaceutical composition having analgesic properties comprising a pharmaceutically acceptable salt of diclofenac and a pharmaceutically acceptable salt of codeine in a weight ratio of about 1:1 to about 3:1. Claim 1. According to Voss et al., the composition can be in the form of a layered tablet with a tablet core prepared from, for example, diclofenac and a coating of, for example, codeine phosphate, compressed onto the core. Col. 2, lines 46-54.

Mok et al. discloses a clinical study that evaluated the analgesic efficacy and safety of the combined use of tramadal (assumed to be tramadol) and diclofenac. During the course of this study, patients received tramadol by one route of administration, intravenously (IV), and diclofenac by another route of administration, intramuscularly (IM). Mok et al. concludes that its "combined use of tramadal and diclofenac produces enhanced analgesic effects."

Addicks et al. discloses a pharmaceutical composition comprising an oral anticoagulant such as warfarin and a platelet inhibitor such as a non-steroidal

anti-inflammatory drug (NSAID). Col. 2, lines 22-25. The NSAID can be aspirin, diclofenac, etc. Col. 2., lines 55-61. According to Addicks et al., the potential exists for a chemical interaction between warfarin and aspirin formulated in a single dosage form. Col. 3, lines 65-68. Thus, Addicks et al. discloses preferred dosage forms wherein physical contact between the warfarin and the aspirin is minimized. For example, Addicks et al. discloses capsules containing aspirin in the form of a plurality of enteric coated microtablets, particles, granules or non-pareils and a warfarin granulation. Col. 4, line 23-col. 5, line 13.

Bergamini et al. is directed to pharmaceutically acceptable opthalmalic and otic formulations including diclofenac and the antibiotic tobramycin. Abstract and col. 6, lines 2-3.

Bodley et al. is directed to an injectable pharmaceutical composition which comprises either diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin, or an inclusion complex of diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin. Col. 1, lines 5-11.

The cited combination of Voss et al., Mok et al., Addicks et al., and Bergamini et al. or Bodley et al. does not render the presently claimed oral administration unit obvious because one of ordinary skill in the art would not have had a rational reason to modify the disclosures of these references as suggested by the Office to arrive at the presently claimed oral administration unit. "[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385, 1396 (2007)(quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). This rational reasoning need not be present in the prior art itself, but must nonetheless exist.

One of ordinary skill in the art would not have had a rational reason incorporate tramadol and diclofenac in a "separated" dosage form of Addicks et al. wherein two active ingredients are formulated such that the physical contact between the two active ingredients is minimized. One of ordinary skill in the art

looking to provide an oral administration form including both tramadol and diclofenac would have simply mixed tramadol and diclofenac and produced a dosage form with a homogeneous mixture of tramadol and diclofenac. One of ordinary skill in the art would not have gone to the trouble to create a more complicated dosage form such as the "separated" dosage form of Addicks et al. This is because one of ordinary skill in the art would not have had a rational reason separate tramadol and diclofenac.

Addicks et al.'s dosage form is designed to prevent a known chemical interaction between two active agents, warfarin and aspirin. But none of the cited references disclose or suggest that tramadol and diclofenac interact chemically or physically. While the Office cites references that show diclofenac interacts with other compounds, such as tobramycin, the Office does not cite any reference that shows diclofenac interacts negatively with tramadol. The cited references certainly do not disclose or suggest the solubility problem associated with combining tramadol and diclofenac discovered by Appellants.

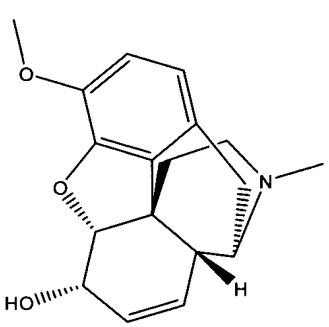
Voss et al., Addicks et al., Bergamini et al. and Bodley et al. cannot possibly disclose or suggest any interactions, such the negative solubility interaction discovered by Appellants, between tramadol and diclofenac. This is because none of Voss et al., Addicks et al., Bergamini et al. and Bodley et al. discloses the specific combination of tramadol and diclofenac.

Similarly, Moks et al. does not disclose or suggest any interaction between tramadol and diclofenac. Furthermore, Moks et al. administers tramadol and diclofenac simultaneously, but via different routes of administration, and neither of the administration routes includes oral administration. Since the solubility problem occurs when both tramadol and diclofenac are formulated for oral administration, Moks et al. does not disclose or suggest the solubility problem.

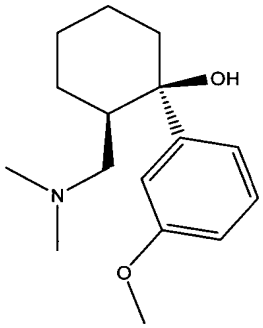
Due to the lack of any disclosure of any undesirable interaction between tramadol and diclofenac in the cited references, in contrast to the undesirable interaction between warfarin and aspirin disclosed in Addicks et al., one of ordinary skill in the art would not have had a rational reason to utilize a "separated" dosage form of Addicks et al. for tramadol and diclofenac.

Moreover, any interactions between the drug combinations disclosed in Voss et al., Addicks et al., Bergamini et al., and Bodley et al. cannot be extrapolated to the combination of tramadol and diclofenac. Since interactions occurring with these drug combinations cannot be extrapolated to the combination of tramadol and diclofenac, one of ordinary skill in the art would not have had a rational reason to utilize a "separated" dosage form of Addicks et al. for tramadol and diclofenac.

Voss et al. discloses the combination of diclofenac and codeine. Although codeine is an opioid and tramadol exhibits opioid activity, their chemical structures are significantly different as illustrated below:



codeine

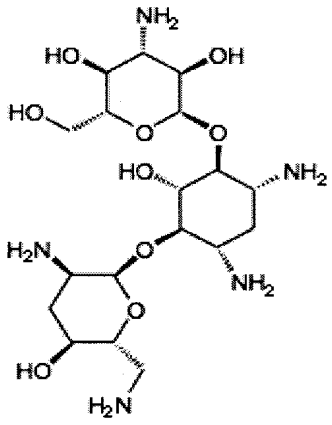


tramadol

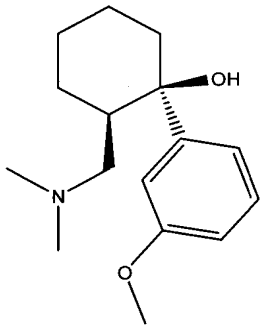
One of ordinary skill in the art understands that any interactions that occur between two compounds, such as interactions which have an effect on their solubility, result from the particular chemical structures of the two compounds. Thus, any interactions between diclofenac and codeine, including interactions that effect solubility, cannot also be expected from the combination of diclofenac and tramadol.

Addicks et al. discloses the combination of warfarin and aspirin. Warfarin and aspirin are structurally completely different from tramadol and diclofenac. Thus, any interactions between warfarin and aspirin, including interactions that effect solubility, cannot also be expected from the combination of diclofenac and tramadol.

Bergamini et al. discloses the combination of diclofenac and tobramycin. According to Bergamini et al., there is an interaction between diclofenac and tobramycin that forms an insoluble complex and effects their solubility. See col. 6, line 10-col. 7, line 30. But tobramycin has a completely different structure than tramadol as illustrated below:



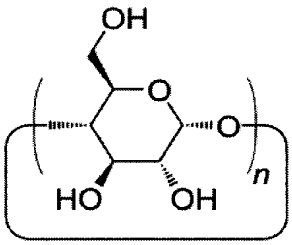
Tobramycin



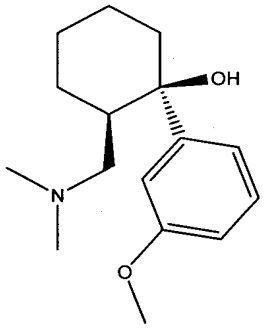
tramadol

In contrast to tramadol, tobramycin does not contain an aromatic moiety. Rather, tobramycin is based on amino glycosidyl groups. Tobramycin has 5 free amino groups and 5 free hydroxyl groups, whereas tramadol only bears one hydroxyl group. The interaction of tobramycin and diclofenac is related to the structure of tobramycin. Due to the difference in structure between tramadol and tobramycin, any interaction between diclofenac and tobramycin cannot also be expected from the combination of tramadol and diclofenac.

Bodley et al. discloses the combination of diclofenac and 2-hydroxypropyl beta-cyclodextrin. According to Bodley et al., there is an interaction between diclofenac and cyclodextrins, including 2-hydroxypropyl beta-cyclodextrin, that increases the solubility of diclofenac. See col. 1, line 44-col. 2, line 10 and col. 3, lines 62-67. But the structure of a cyclodextrin is completely different than the structure of tramadol as illustrated below:



Cyclodextrin



tramadol

In contrast to tramadol, a cyclodextrin does not contain an aromatic moiety. A single unit of a cyclodextrin contains 3 free hydroxyl groups. A ß-cyclodextrin, which is derived from 7 of these units, contains 21 free hydroxyl groups. Tramadol only bears one hydroxyl group. Hydroxyl groups can form hydrogen bonds which influence the solubility of a compound. Thus, the structure of cyclodextrin can explain its effect on the solubility of diclofenac. However, due to the difference in structure between tramadol and cyclodextrin, any interaction between diclofenac and cyclodextrin cannot also be expected from the combination of tramadol and diclofenac.

Similarly, one of ordinary skill in the art would not have had a rational reason to replace the codeine in the layered tablet of Voss et al. with tramadol from Mok et al. As discussed above, one of ordinary skill in the art looking to provide an oral administration form including both tramadol and diclofenac would have simply mixed tramadol and diclofenac and produced a dosage form with a homogeneous mixture of tramadol and diclofenac. One of ordinary skill in the art would not have gone to the trouble to create a more complicated dosage form such as the layered tablet disclosed in Voss et al. This is because none of the references cited disclose or suggest any interactions between tramadol and diclofenac or any problems with formulating the combination of tramadol and diclofenac, such as the solubility problem associated with combining tramadol and diclofenac discovered by Appellants, as explained above.

Only the Appellants' own application provides a reason to combine Voss et al., Moks et al., Addicks et al., and Bergamini et al. or Bodley et al. to arrive at

the presently claimed oral administration unit. But an obviousness rejection should take "into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made" and should "not include knowledge gleaned only from applicant's disclosure." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Accordingly, the cited combination of references does not render the presently claimed oral administration unit *prima facie* obvious.

Moreover, any *prima facie* case of obviousness over Voss et al. in view of Mok et al and Addicks et al., and Bergamini et al. or Bodley et al. is effectively rebutted by the unexpected results (i.e. the unimpaired release profiles and the retained bioavailabilities of tramadol and diclofenac) associated with the presently claimed oral administration unit. The unimpaired release profiles, and consequently, the retained bioavailabilities are unexpected for the following reasons: (1) tramadol and diclofenac are present together in the gastrointestinal tract after administration of the presently claimed oral administration unit; and (2) this presence of tramadol and diclofenac together could lead to the formation of the observed sparingly soluble compound. The experimental data provided in the specification demonstrates these unexpected results.

The table on page 11 and Figure 1 show the release profile for a capsule commensurate in scope with the presently claimed oral administration unit. The capsule contained retarded release tramadol-HCl pellets and retarded release diclofenac-Na pellets such that the capsule contained a quantitative ratio of tramadol to diclofenac of 3:2 (75 mg tramadol-HCl:50 mg diclofenac-Na). According to the table and Figure 1, 79% tramadol and 71% diclofenac were released after 8 hours (480 min).

Figure 2 shows the release profile for a conventional common matrix tablet containing tramadol-HCl and diclofenac-Na where the tablet contained a quantitative ratio of tramadol to diclofenac of 3:2 (75 mg tramadol-HCl:50 mg diclofenac-Na). According to Figure 2, far less tramadol and diclofenac were released after 8 hours compared to the capsule of the present application. In

particular, only about 45% tramadol and about 10% diclofenac were released after 8 hours.

Figure 3 shows the release profile for retarded release diclofenac pellets. According to Figure 3, about 71% diclofenac was released after 8 hours. Similarly, Figure 4 shows the release profile for retarded release tramadol pellets. According to Figure 4, about 79% tramadol was released after 8 hours. Comparing Figure 2 with Figures 3 and 4 demonstrates that the conventional matrix tablet impairs the release profiles of tramadol and diclofenac, and consequently impairs their bioavailabilities.

Comparing Figure 1 with Figure 2 illustrates that the presently claimed oral administration unit does not impair the release profiles or reduce the bioavailabilities of the tramadol and diclofenac, respectively. Furthermore, comparing Figure 1 with Figures 3 and 4 demonstrates the presently claimed oral administration unit provides release profiles for tramadol and diclofenac that correspond to release profiles of an administration unit containing tramadol only and an administration unit containing diclofenac only. Thus, the presently claimed oral administration unit does not reduce bioavailabilities.

In sum, Voss et al. in view of Mok et al. and Addicks et al., and Bergamini et al. or Bodley et al. does not render the presently claimed oral administration unit *prima facie* obvious. Even assuming they provided a proper *prima facie* case of obviousness, the unexpected results associated with the presently claimed oral administration unit effectively rebuts such a *prima facie* case. Therefore, Appellants respectfully request the Board to reverse the rejection of claims 1-4, 6, 7, 9-26 and 29 under 35 U.S.C. § 103(a) over Voss et al. in view of Mok et al and Addicks et al., and Bergamini et al. or Bodley et al.

Rejection under 35 U.S.C. § 103(a) over Raffa in view of Mok et al. and Addicks et al., and Bergamini et al. or Bodley et al.

Claims 1-4, 6, 7, 9-26 and 29

Raffa discloses a composition comprising a tramadol material and a non-steroidal anti-inflammatory drug (NSAID). Col. 3, lines 16-17.

According to Raffa, the NSAID and the tramadol material are generally present in a weight ratio of tramadol material to NSAID from about 1:1 to 1:200. Col. 4, lines 41-44. Raffa provides an exhaustive list of NSAIDs that can be used in the composition including diclofenac. Col. 3, line 60-col. 4, line 36. Importantly, Raffa discloses intimately mixing the tramadol material and the NSAID to prepare the pharmaceutical composition. Col. 5, lines 22-26. Raffa does not disclose or suggest separating tramadol and the NSAID (e.g. diclofenac) into separate subunits and also discloses some embodiments (e.g. oral liquid preparations, aerosol) where tramadol and diclofenac could not be separated into separate subunits.

One of ordinary skill in the art would not have had a rational reason incorporate tramadol and diclofenac from Raffa in a "separated" dosage form of Addicks et al. wherein two active ingredients are formulated such that the physical contact between the two active ingredients is minimized. One of ordinary skill in the art looking to provide an oral administration form including both tramadol and diclofenac would have simply mixed tramdol and diclofenac and produced a dosage form with a homogeneous mixture of tramadol and diclofenac as disclosed in Raffa. One of ordinary skill in the art would not have gone to the trouble to create a more complicated dosage form such as the "separated" dosage form of Addicks et al. This is because, for the same reasons discussed above and since Raffa does not disclose or suggest any interactions between or problems with combining tramadol and diclofenac, one of ordinary skill in the art would not have had a rational reason separate tramadol and diclofenac.

Only the Appellants' own application provides a reason to combine Raffa, Moks et al., Addicks et al., and Bergamini et al. or Bodley et al. to arrive at the presently claimed oral administration unit. But an obviousness rejection should take "into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made" and should "not include knowledge gleaned only from applicant's disclosure." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Accordingly, the cited

combination of references does not render the presently claimed oral administration unit *prima facie* obvious.

Furthermore, any *prima facie* case of obviousness over Raffa in view of Mok et al. and Addicks et al., and Bergamini et al. or Bodley et al. is effectively rebutted by the unexpected results (i.e. the unimpaired release profiles and the retained bioavailabilities of tramadol and diclofenac) associated with the presently claimed oral administration unit. As discussed above, the experimental data provided in the specification demonstrates these unexpected results.

Therefore, Appellants respectfully request the Board to reverse the rejection of claims 1-4, 6, 7, 9-26 and 29 under 35 U.S.C. § 103(a) over Raffa in view of Mok et al and Addicks et al., and Bergamini et al. or Bodley et al.

VIII. CLAIMS APPENDIX

See the attached Claims Appendix for a copy of the claims involved in the appeal.

IX. EVIDENCE APPENDIX

See the attached Evidence Appendix.

X. RELATED PROCEEDINGS APPENDIX

See the attached Related Proceedings Appendix.

XI. CONCLUSION

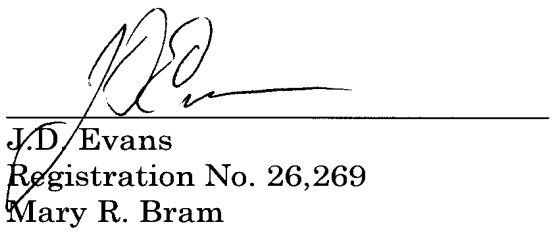
For the foregoing reasons, the obviousness rejections of Appellants' claims 1-4, 6, 7, 9-26 and 29 are improper and should be reversed.

The Appeal Brief is submitted with the required fee of $620.00. This amount is believed to be correct, however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 05-1323, (Docket No.: 029310.50777CP).

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No.: 029310.50777CP).

Respectfully submitted,

October 31, 2011



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CLAIMS APPENDIX

The Appealed Claims

1. An oral administration unit comprising a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second active substance diclofenac or a pharmaceutically acceptable salt thereof, wherein:

the two active substances are present in separate subunits so as to not impair the release profiles of the two active substances;

the separate subunits are present in multiparticulate form;

the active substances tramadol and diclofenac are contained in a quantitative ratio of 1:4 to 4:1; and

the tramadol and the diclofenac are released in amounts of more than 70% and more than 60% by weight, respectively, within 8 hours.

2. An oral administration unit according to claim 1, wherein the first active substance is a pharmaceutically acceptable salt of tramadol selected from the group consisting of tramadol hydrochloride, tramadol hydrobromide, tramadol sulfate, tramadol phosphate, tramadol fumarate, tramadol succinate, tramadol maleate, tramadol nitrate, tramadol acetate, tramadol propionate, tramadol malonate, tramadol citrate, tramadol tartrate, tramadol benzoate, tramadol salicylate, tramadol phthalate and tramadol nicotinate, and the second active substance is a pharamaceutically acceptable salt of diclofenac selected from the group consisting of diclofenac-sodium, diclofenac-potassium, diclofenac-calcium, diclofenac-magnesium and diclofenac-cholestyramine.

3. An oral administration unit according to claim 2, wherein the pharmacologically acceptable salt of tramadol is tramadol-HCl.

4. An oral administration unit according to claim 2, wherein the pharmacologically acceptable salt of diclofenac is diclofenac-Na.

6. An oral administration unit according to claim 5, wherein the quantitative ratio of tramadol to diclofenac is 1:2 to 3:1.

7. An oral administration unit according to claim 6, wherein the quantitative ratio of tramadol to diclofenac is 1:1 to 2.5:1.

9. An oral administration unit according to claim 1, wherein the subunits are each present in a form independently selected from the group consisting of microtablets, microcapsules, ion-exchange resinates, granules, active substance crystals, and pellets.

10. An oral administration unit according to claim 9, wherein the subunits are each present in the form of pellets or composite pellets produced by extrusion or spheronisation.

11. An oral administration unit according to claim 1, wherein at least one of the two active substances is present in a controlled release formulation.

12. An oral administration unit according to claim 11, wherein both active substances are present in a controlled release formulation.

13. An oral administration unit according to claim 11, wherein the controlled release formulation is effected via coating the at least one active substance, binding the at least one active substance to an ion-exchange resin, embedding the at least one active substance in a controlled release matrix, or a combination thereof.

14. An oral administration unit according to claim 13, wherein the at least one active substance is coated with a coating of a water-insoluble polymer or wax.

15. An oral administration unit according to claim 14, wherein the at least one active substance is coated with a water-insoluble polymer selected from the group consisting of polyacrylate resins and cellulose derivatives.

16. An oral administration unit according to claim 15, wherein the at least one active substance is coated with a water-insoluble alkylcellulose.

17. An oral administration unit according to claim 14, wherein the at least one active substance is coated with a water-insoluble ethylcellulose or poly(meth)acrylate polymer.

18. An oral administration unit according to claim 13, wherein the controlled release formulation is effected by embedding the at least one active substance in a controlled release matrix.

19. An oral administration unit according to claim 11, wherein the oral administration unit further comprises at least one of the active substances in a non-controlled release form.

20. An oral administration unit according to claim 1, wherein the oral administration unit is a sachet, a capsule or a tablet.

21. An oral administration unit according to claim 20, wherein the oral administration unit is a capsule or a pellet tablet.

22. An oral administration unit according to claim 20, wherein the oral administration unit is a rapidly decomposing tablet.

23. An oral administration unit according to claim 22, wherein the oral administration unit is a rapidly decomposing pellet tablet.

24. An oral administration unit according to claim 20, further comprising a release layer that effects a dissociation of the subunits from one another on contact with an aqueous body fluid.

25. An oral administration unit according to claim 20, wherein the oral administration unit is a tablet having a score mark to facilitate subdivision of the tablet.

26. An oral administration unit according to claim 20, wherein the oral administration unit has a gastric juice-resistant coating.

29. An oral administration unit according to claim 27, wherein the oral administration unit is a capsule.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.